

Supporting Information

# Optimizing Solvent Selection and Processing Conditions to Generate High Bulk-Density, Co-Precipitated Amorphous Dispersions of Posaconazole

Derek Frank<sup>1,\*</sup>, Luke Schenck<sup>1</sup>, Athanas Koynov<sup>1</sup>, Yongchao Su<sup>2</sup>, Yongjun Li<sup>2</sup>, Narayan Variankaval<sup>2</sup>

<sup>1</sup> Process Research & Development, Merck & Co., Inc, Rahway, NJ 07065, USA

<sup>2</sup> Analytical Research & Development, Merck & Co., Inc, Rahway, NJ 07065, USA

\* Correspondence: derek.frank@merck.com

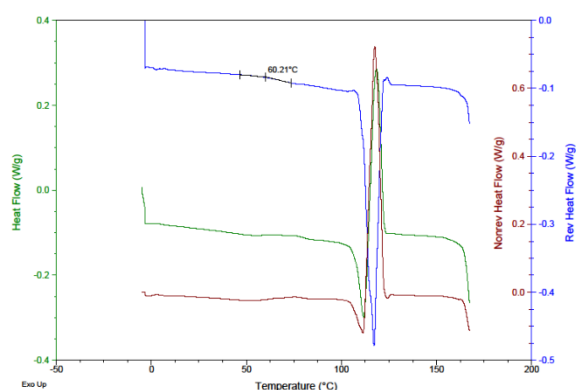


Figure S1. mDSC of Form III posaconazole showing contamination by amorphous posaconazole, apparent by its  $T_g$  at 60 °C.

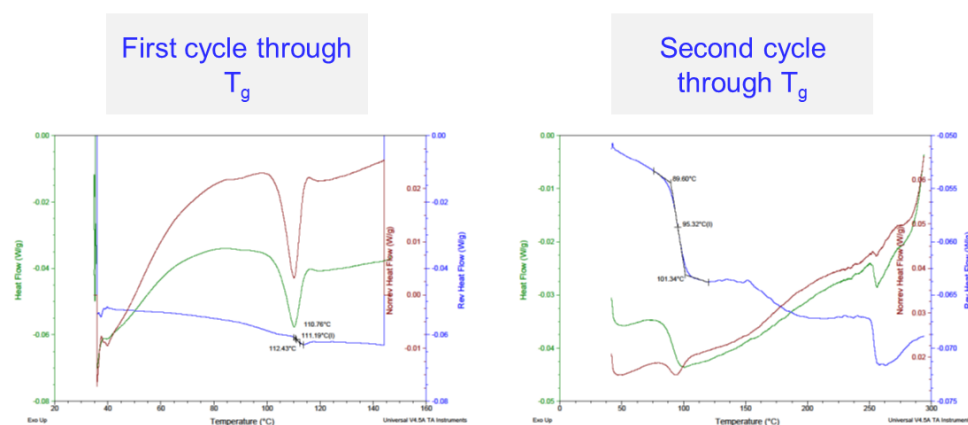


Figure S2. Thermogram through  $T_g$  for posaconazole/HPMCAS dispersion generated by precipitation from MEK into *n*-heptane before (first cycle) and after (second cycle) heating to 150 °C.

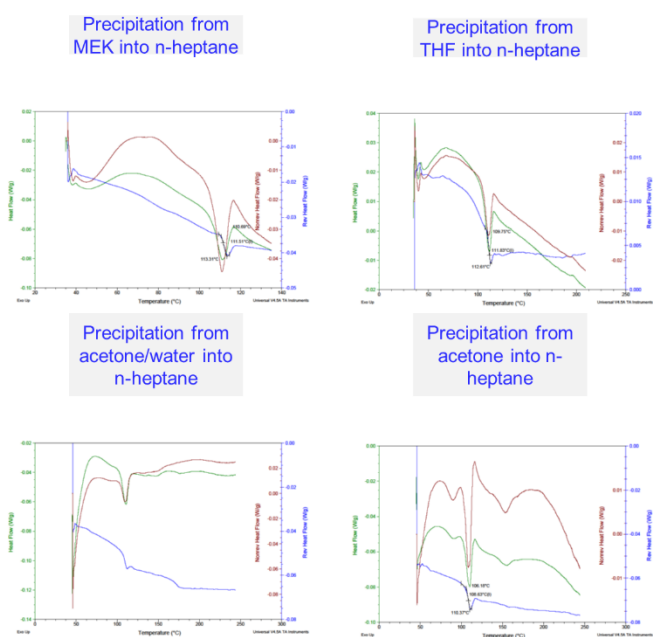
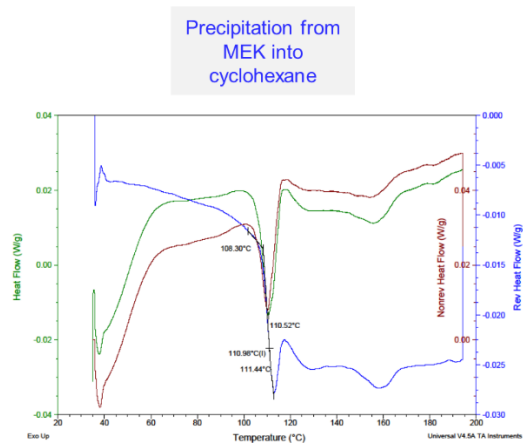
Figure S3. Posaconazole/HPMCAS co-precipitates generated using *n*-heptane as anti-solvent.

Figure S4. Posaconazole/HPMCAS co-precipitate generated using cyclohexane as anti-solvent.

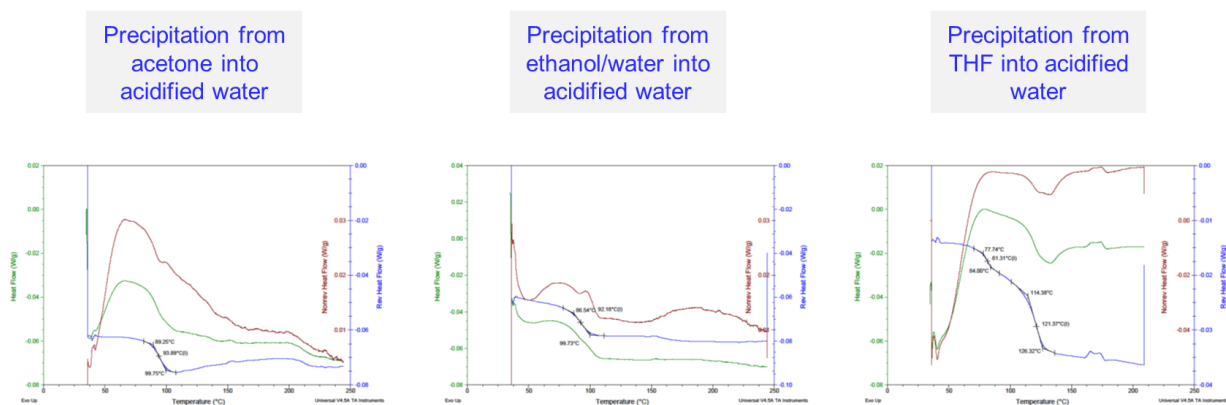


Figure S5. Posaconazole/HPMCAS co-precipitates generated using 0.001 N HCl as anti-solvent.

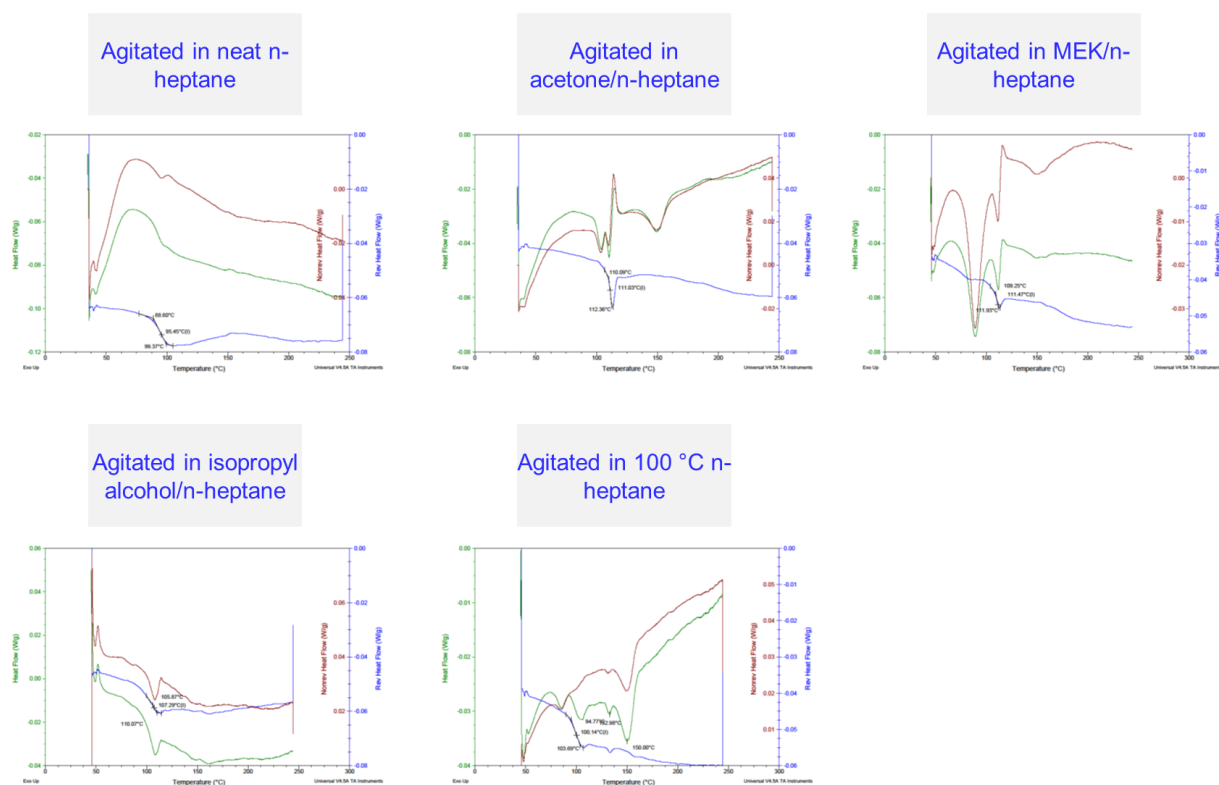
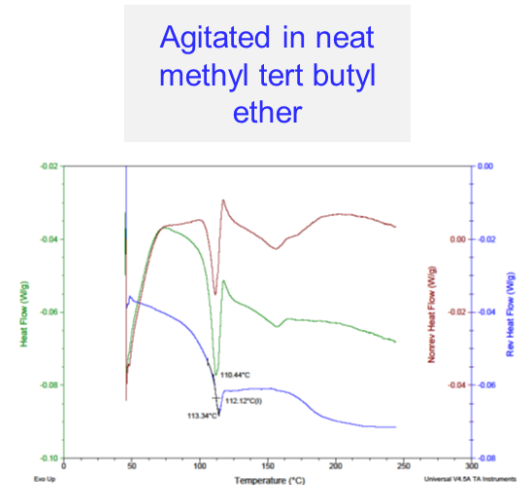
Figure S6. Amorphous posaconazole cPAD re-suspended in *n*-heptane and binary solvent mixtures.

Figure S7. Amorphous posaconazole cPAD re-suspended in MTBE.

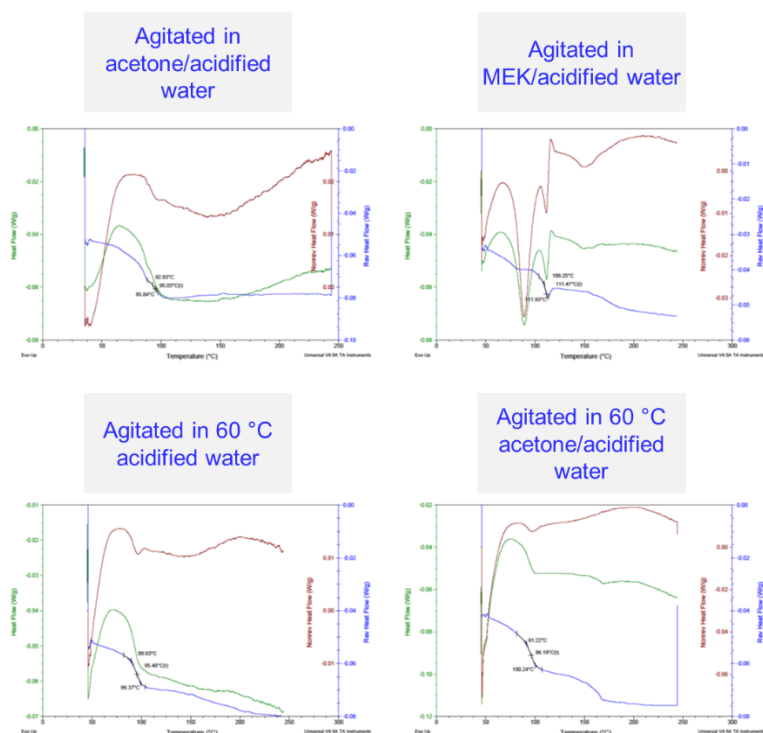


Figure S8. Amorphous posaconazole cPAD re-suspended in 0.001 N HCl and binary solvent mixtures.

### Dynochem prediction

Activity coefficients of acetone in binary solvent mixtures in a) water and b) *n*-heptane as predicted in Dynochem using the NRTL feature.

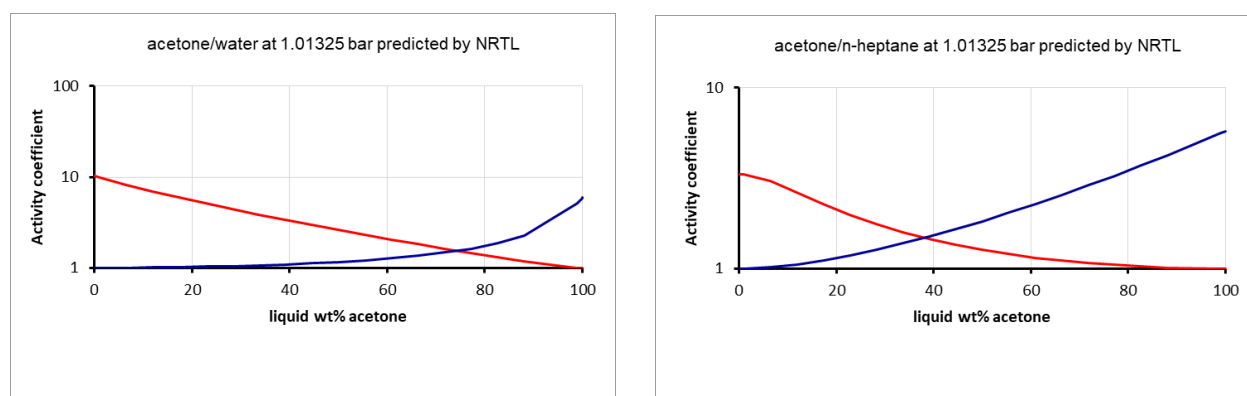


Figure S9. Activity coefficients of acetone in binary solvent mixtures in a) water and b) *n*-heptane as predicted in Dynochem.

### Scanning electron microscopy

Particle morphology was assessed by scanning electron microscopy using a Tabletop Microscope TM3030 (Hitachi High-Technologies Co., Tokyo, Japan) at 15 kV acceleration voltage.

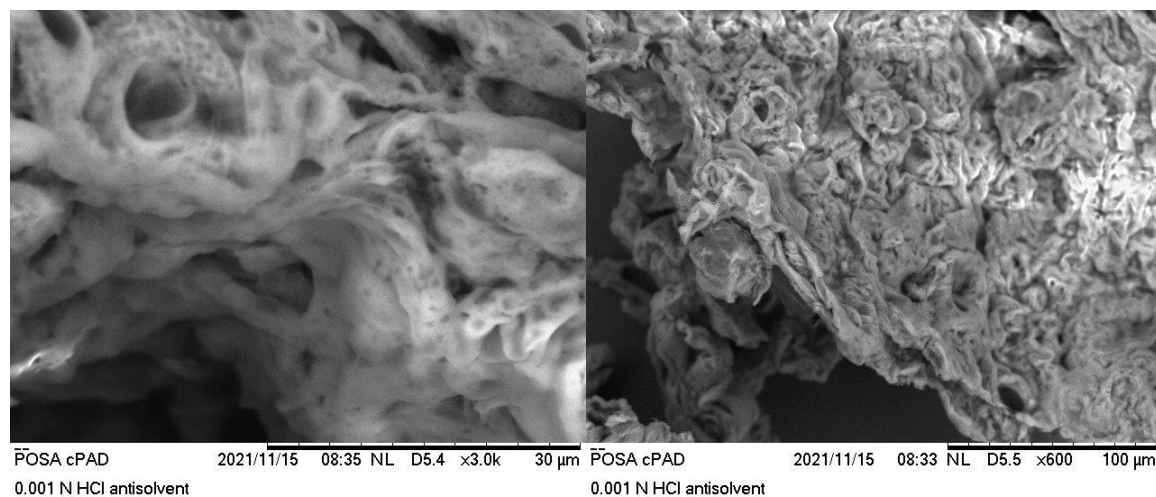


Figure S10. Scanning electron microscopy of posaconazole cPAD generated by precipitation into 0.001 N HCl.

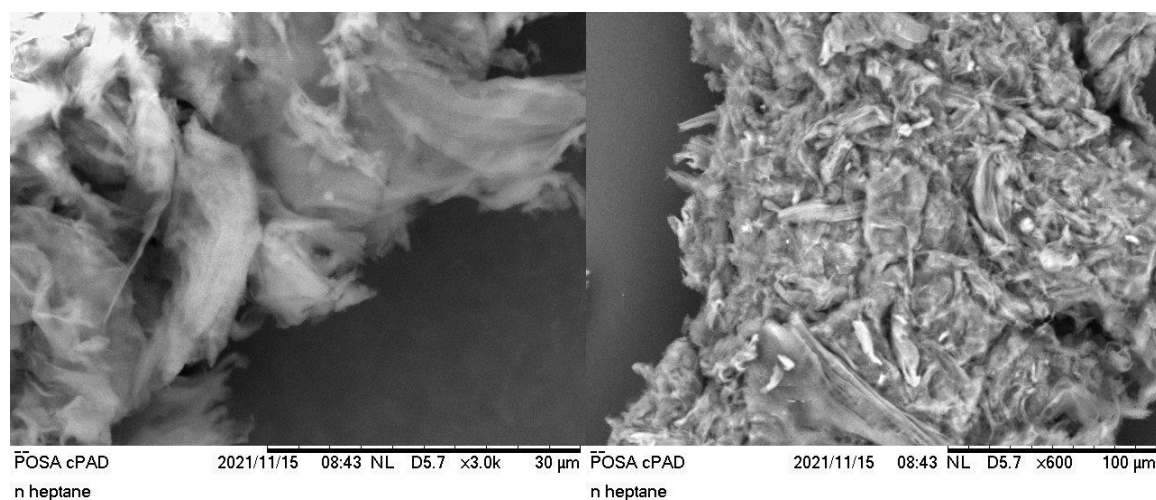


Figure S11. Scanning electron microscopy of posaconazole cPAD generated by precipitation into *n*-heptane.

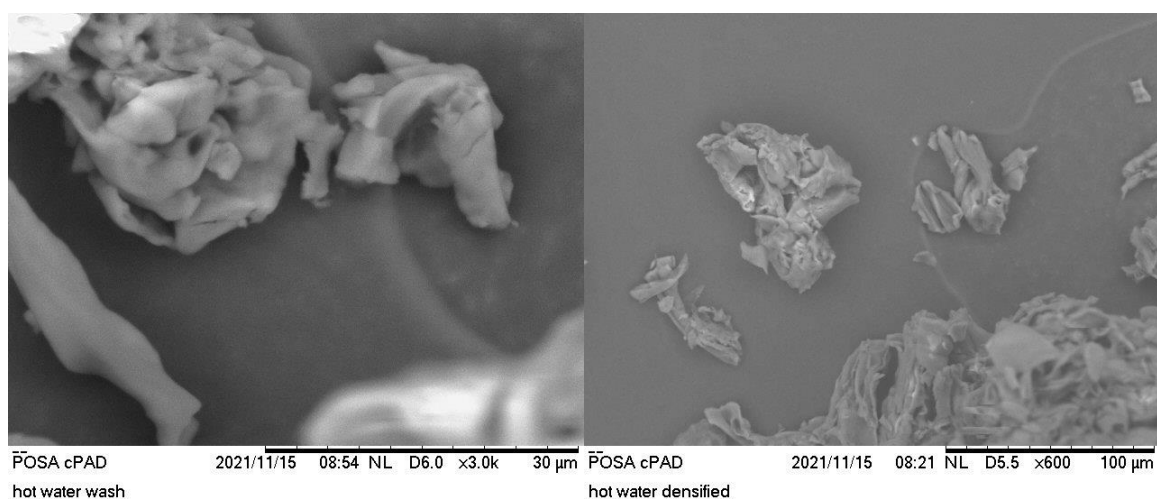


Figure S12. Scanning electron microscopy of posaconazole cPAD generated by precipitation into 0.001 N HCl and washed with 60 °C acidified water.